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Calcineurin Inhibitor–Free Immunosuppression in Renal Transplantation

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ABSTRACT

Purpose. To describe our initial results using a calcineurin inhibitor–free immunosuppression protocol in renal transplants.

Patients and methods. Between October 2001 and June 2003, 56 recipients of a renal allografts were started on an immunosuppression protocol without calcineurin inhibitors, consisting of basiliximab, sirolimus, mycophenolate mofetil, and steroids. We analyzed patient and graft survival, acute rejection episodes, and renal function.

Results. The mean follow-up was 19.6 months. Actuarial patient survival at 1 and 2 years was 98.1% and 95.3%, respectively. Actuarial graft survival at 1 and 2 years was 92.9% and 87.6%, respectively. Acute rejection occurred in 27.8% of the patients, usually Banff 1 (73.3%). There was stable renal function with mean serum creatinine of 1.3, 1.4, 1.3, and 1.3 mg/dL at 1, 6, 12, and 24 months after transplant.

Conclusions. The use of immunosuppression free of calcineurin inhibitors is effective and safe. Further follow-up is needed to evaluate the impact on long-term results.

KIDNEY TRANSPLANT OUTCOMES have steadily improved over the past decade[1] due to modern immunosuppression protocols and better prophylaxis and treatment of common posttransplant infections.[2] The introduction of calcineurin inhibitors (CNIs)—cyclosporine (CsA) and tacrolimus (Tac)—in the last two decades has resulted in a significant decrease in acute rejection and an improvement in short-term graft survival[3] with most centers now achieving 85% to 90% 1-year graft survival.[4] However, long-term graft loss due to chronic allograft nephropathy (CAN) remains a major problem in renal transplantation.[5] While there appear to be many contributors to CAN, many studies emphasize the nephrotoxicity associated with CNIs.[6–8] Several studies of CNI-free immunosuppression[2,9–13] or early CsA withdrawal[14–16] have been reported, with good patient and graft survival and without drug-induced nephrotoxicity. In this report, we describe our initial results using a CNI-free immunosuppression protocol in renal transplants.

PATIENTS AND METHODS

Between October 2001 and June 2003, 56 recipients of a first renal allograft were enrolled in this prospective study, which had obtained local ethics committee approval and written informed consent from each patient. Exclusion criteria consisted of prior transplantation or exposure to immunosuppressants, type I diabeties, severe hyperlipidemia prior to transplantation (serum cholesterol level greater than 350 mg/dL or serum triglycerides over 400 mg/dL), white blood cells less than 3000/mm^3, or platelets less than 100,000/mm^3.

Immunosuppressive protocol included basiliximab 20 mg (days 0 and 4), mycophenolate mofetil (1 g two times per day), steroids, and sirolimus (5 mg daily after a 20 mg loading dose). Sirolimus doses were then adjusted to achieve target through levels between 10 and 15 ng/mL for 6 months and 5 to 10 ng/mL thereafter. All clinical rejections were biopsy-proven and Banff scored prior to initiation of therapy with high-dose steroids. Primary endpoints of the study were patient survival, graft survival, and the number of acute rejection episodes. Secondary endpoints included delayed graft function, serum creatinine, and calculated creatinine clearance.

Statistical analysis was performed using SPSS for Windows 10.0. Descriptive statistics are presented as mean values and standard deviations for the continuous variables and as frequencies and percentages for the categorical variables. Groups were compared using Student t test for continuous variables and χ^2 testing for categorical parameters. Graft and patient cumulative actuarial survivals were calculated by Kaplan-Meier analysis and tested for

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Table 1. Patient Characteristics at the Time of Renal Transplantation

Mean age ± SD (y)	39.4 ± 12.7
Sex (male/female)	40/6
Cause of renal failure (%)	
Glomerulonephritis	31.5
Tubulointerstitial disease	16.7
Diabetes/hypertension	14.8
Polycystic disease	13.0
Other/not determined	24.0
Graft: cadaveric/living donor	47 (83.9%)/9 (16.1%)
HLA mismatches	3.12 ± 0.84
Cold ischemia (h)	18.1 ± 7.7
Donor age (y)	39.9 ± 16.2

differences with the Mantel-Cox log-rank test. Results were considered statistically significant if the *P* value was less than or equal to .05.

RESULTS

Patient characteristics at baseline are shown in Table 1. Mean follow-up was 19.6 months (range: 1 to 32.2 months). Actuarial patient survival at 1 and 2 years was 98.1% and 95.3%, respectively. Actuarial graft survival at 1 and 2 years was 92.9% and 87.6%, respectively. There were seven graft losses, two due to chronic dysfunction, two due to vascular complications, and three to death with a functioning graft. When observations were censored for patients dying with a functioning graft, actuarial graft survival at 1 and 2 years was 94.6% and 91.9%, respectively. Acute rejection occurred in 27.8% of patients, mostly Banff 1 (73.3%). Overall, Banff 2 and 3 acute rejection occurred in 7.4% of the patients. All episodes were reversed with steroids. Actuarial graft survival at 1 and 2 years was 93.3% and 93.3%, when acute rejection occurred; and 97.4% and 89.5% among patients without acute rejection, a difference that was not statistically significant. There was delayed graft function in 16.7% of the transplants, but it did not influence graft survival at 1 and 2 years. There was a stable renal function with mean serum creatinine of 1.3, 1.4, 1.3, and 1.3 mg/dL at 1, 6, 12, and 24 months after the transplant. One-year mean serum creatinine level was significantly lower in rejection-free patients (1.2 ± 0.4 mg/dL) than in those who suffered an acute rejection (1.6 ± 0.8 mg/dL, $P = .031$).

DISCUSSION

Graft survival in renal transplantation is influenced by multiple risk factors, including donor and recipient age, acute rejection, human leukocyte antigen (HLA) mismatches, and comorbidity.[15] Despite the significant improvements in short-term graft survival and the reduction of acute rejection episodes with CsA and Tac, these CNIs contribute to CAN.[5] They decrease glomerular filtration rate, increase blood pressure and hyperlipidemia, and may lead to interstitial fibrosis, with a major negative impact on long-term results. The increasing use of expanded or marginal donors, probably more susceptible to CNI nephrotoxicity,[10] has emphasized the need to find safer immunosuppressive protocols that both provide protection against acute rejection episodes and permit recovery of graft function after the transplant.[2] The introduction of sirolimus has allowed the use of immunosuppression protocols without CNIs[2,9–13] or with early CsA withdrawal[14–16] with good patient and graft survival and improved renal histology and function.[14] In our experience, CNIs free immunosuppression was associated with good 1- and 2-year patient and graft survivals. Although our acute rejection rate (27.8%) was slightly higher than some recent reports in the literature,[5,15,16] the incidence of Banff 2 or 3 acute rejections was low (7.4%) and did not influence graft survival. Renal function, as evidenced by serum creatinine values, was stable during our study, although slightly better among rejection-free patients (1.2 ± 0.4 mg/dL) than those who suffered acute rejection (1.6 ± 0.8 mg/dL, $P = .031$).

In conclusion, in our short experience, the use of immunosuppression free of CNIs is effective, with good graft and patient outcomes, and safe. Further follow-up is needed to see the impact of this protocol and of the acute rejection episodes on long-term results.

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